ABSTRACT

Pharmacodynamic modeling of the PK/PD index fAUC/MIC* and tAUC/MIC* demonstrated that they better describe the in vivo efficacy of NOSO-502 against EC and KPN isolates in the neutropenic thigh model. The fAUC/MIC* index is visualized in the parameter space. These PK/PD targets will be important in integrating human PK exposures to treatment.

METHODS

Stages of susceptibility testing for NOSO-502 against study organisms:

RESULTS

Pharmacodynamic Index Determination: The dose-response curve and impact of dose fractionation on the in vivo efficacy of NOSO-502 is shown for EC 25922. Doses were administered in one, two, or four doses over a 24 h treatment period. Each symbol is the organism burden in one thigh. The exposure-response relationship between each of these PD indices is shown. The curve through the data points represent the best-fit curve based on the hill equation. The coefficient of determination (R²), Emax, maximal effect (ED50), and slope of the curve (h) is shown for each PD index.

RESULTS (cont.)

Pharmacodynamic Target: The in vivo pharmacodynamic modeling of the PD index fAUC/MIC* and tAUC/MIC* demonstrates that they better describe the in vivo efficacy of NOSO-502 against EC and KPN isolates in the neutropenic thigh model. These PD indices are important in integrating human PK exposures to treatment and will be used for clinical trials.

CONCLUSIONS

1) NOSO-502, a first-in-class odilorhabdin antibiotic, demonstrated in vivo efficacy against EC and KPN isolates including beta-lactamase resistance mechanisms. The PK/PD index fAUC/MIC* may be the best-fit index based on the R² values.

2) NOSO-502 efficacy was dose-dependent and AUC/MIC* was the PK/PD index that most robustly predicted the efficacy.

3) NOSO-502 PD target free AUC/MIC* for net stasis and 1-log kill for EC and KPN.

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